FDA Questions for Circulatory System Devices Panel
October 26, 2011
P100046 - AtriCure Synergy Ablation System

1. PRIMARY SAFETY ENDPOINT RESULTS

The primary safety endpoint was the rate of Major Adverse Events (MAEs) occurring within the initial 30 days post procedure or discharge (whichever was later). These MAEs consisted of: Death, Excessive Bleeding (defined as > 2 units of RBCs with reoperation), Stroke, TIA or MI. The performance goal was 18.95% based on a historical rate of 13.95%. The primary safety endpoint would be considered met if the posterior probability that the rate of MAE is less than 18.95% exceeds 0.95. The safety results are summarized in the following table.

Primary Safety Endpoint – Composite MAE within 30 days	% (n/N)	BCI	Posterior Probability that MAE rate < 18.95%
Treated patients	9.1% (5/55)	(0.00, 0.179)	0.967
Non-Paroxysmal Patients	9.8% (5/51)	(0.00, 0.192)	0.946

Q1. The primary safety results were borderline with respect to the pre-specified performance goal. None of the MAEs observed in the study were adjudicated to be related to the device, with one bleeding event considered related to the ablation procedure.

Although not part of the primary safety endpoint, 8 serious adverse events that occurred within the 30-day follow-up period were determined to be related to the AF ablation procedure (1 atrial rupture, 3 AV block, 1 bradycardia, 1 vena cava injury, and 1 venous injury) for a rate of device- or ablation procedure-related serious adverse events of 14.5%.

Please provide your interpretation of the primary safety results.

2. PRIMARY EFFECTIVENESS ENDPOINT RESULTS

The primary effectiveness endpoint was defined as freedom from AF at 6-months, off anti-arrhythmic drugs (AADs). Freedom from AF was defined as no episode of AF lasting longer than 5 minutes on 24-hour Holter. The pre-defined performance goal for the primary effectiveness endpoint is 60%, which is based on a historical rate of 70%. The primary effectiveness endpoint would be considered met if the posterior probability that the rate of subjects AF-free at 6-months, off AADs, is greater than 60% exceeds 0.975.

Primary Effectiveness Endpoint – Freedom from AF at 6 months, off AADs	% (n/N)	BCI	Posterior Probability that the Primary Effectiveness Success Rate is > 60%
Treated Patients	74.0% (37/50)	(0.604, 1.00)	0.978
Non-Paroxysmal Patients	73.9% (34/46)	(0.597, 1.00)	0.972

Similar to the safety results, when considering only non-paroxysmal subjects, the primary effectiveness endpoint is not met.

FDA believes the following factors may affect the interpretability of the effectiveness results:

- Inadequate drug washout at the 6 month Holter evaluation
- Cardioversions performed during the follow-up period
- Lesion set deviations
- Current clinical guidelines stating that occurrence of all tachyarrhthmias > 30 seconds should be considered treatment failures

Q2. Please provide your interpretation of the primary effectiveness results considering the factors summarized on the following table which presents the primary effectiveness results when the inadequate drug washout, late cardioversions, alternate methods of lesion creation, and current definitions of treatment failure are considered.

	Treated	Non-Paroxysmal
Effectiveness Endpoint	**% (n/N)**	**% (n/N)**
Effectiveness Evaluable at 6-Month Follow-up	N=50	N=46
PRIMARY ANALYSIS		
Primary Effectiveness Endpoint – (Freedom from AF at 6 months, off AADs)	**74.0% (37/50)**	**73.9% (34/46)**
Failure by rhythm	10.0% (5/50)	8.7% (4/46)
Failure by AAD	16.0% (8/50)	17.4% (8/46)
ANCILLARY ANALYSIS		
Free of AF, AFL, and AT and off AADs	**50% (25/50)***	**50% (23/46)***
Failure by rhythm AF Atrial flutter	11 (9) (2)	10 (8) (2)
Failure by AAD Inadequate drug washout	6 (3)	5 (3)
Failure by CV between 3 and 6 months	2	2
Failure by alternate method for lesion creation	8	8
Free of AF, AFL, and AT, regardless of AADs	**58.0% (29/50)**	**56.5% (26/46)**
Failure by rhythm AF Atrial flutter	11 (9) (2)	10 (8) (2)

	Treated	Non-Paroxysmal
Failure by late CV	2	2
Failure by alternate method for lesion creation	8	8

* One patient failed by both late CV and AAD. Another patient failed by both rhythm (AFL) and AAD.

3. STUDY DESIGN & INDICATED POPULATION

The original intent of the study was to enroll subjects who had *permanent AF* according to the 2006 ACC/AHA/ESC Practice Guidelines, which FDA typically interprets as *longstanding persistent AF* per the 2007 HRS Statement. The study actually enrolled a heterogeneous patient population that included 4 subjects with paroxysmal AF, 22 subjects with persistent AF, and 29 subjects with longstanding persistent AF. Because the subjects actually enrolled in the study predominantly had persistent and longstanding persistent AF, FDA and the sponsor agreed to consider the following indications for use statement.

> *The AtriCure Synergy Ablation System is intended to ablate cardiac tissue for the treatment of persistent and longstanding persistent atrial fibrillation in patients who are undergoing open concomitant coronary artery bypass grafting and/or valve replacement or repair.*

Q3. FDA has the following concerns, particularly because of the enrollment of a heterogeneous patient population in the ABLATE study, even though they were part of the original FDA-approved study design:

- ***The follow-up schedule is not designed to assess recurrence in subjects with paroxysms of AF.***
- ***Post-treatment cardioversions were allowed at any time during follow-up, and occurred as short as 9 days prior to the Holter recording.***
- ***Assessment of effectiveness by a single 24-hour Holter recording at 6 months may not be adequate.***

Given the heterogeneous patient population, please comment on whether data from the paroxysmal AF patients enrolled in the ABLATE study should be considered in the evaluation of the proposed indication. In addition, please comment on whether the study design is appropriate for a combination of persistent and longstanding persistent AF populations.

4. ADDITIONAL DATA COLLECTION

The sponsor obtained additional data in support of this PMA after enrollment had been stopped. This additional data collection included Holter data from ABLATE and RESTORE study patients at 12 or more months, an additional cohort of patients from the sponsor's ABLATE AF study, and data from two institutional databases.

Q4. Considering that current guidelines for the evaluation of ablation effectiveness recommend follow-up for a minimum of 12 months, please comment whether the displayed 12-month effectiveness results demonstrate adequate durability of treatment effect to support approval. Please comment on the utility of the ABLATE study alone, as well as data from the other sources, summarized in the following tables for non-paroxysmal subjects.

	ABLATE	ABLATE AF	RESTORE	Wash U	Baylor-Plano
Sample Size (N)	51	13	36	56	8
Primary safety	9.8% (5/51)	0% (0/13)	8.3% (3/36)	14.3% (8/56)	25.0% (2/8)
Death	3.9% (2/51)	0% (0/13)	5.6% (2/36)	3.6% (2/56)	12.5% (1/8)
Bleeding	3.9% (2/51)	0% (0/13)	8.3% (3/36)	8.9% (5/56)	24.0% (2/8)
Stroke/TIA	2.0% (1/51)	0% (0/13)	0.0% (0/36)	1.8% (1/56)	0% (0/11)
MI	0% (0/51)	0% (0/13)	0.0% (0/36)	0% (0/56)	0% (0/11)

	ABLATE	ABLATE AF	RESTORE	Wash U	Baylor-Plano
AF Free @ 6 months, off AADs	73.9% (34/46)	81.8% (9/11)	64.3% (18/28)	74.5% (35/47)	0% (0/2)
AF Free @ 6 months	82.6% (38/46)	90.9% (10/11)	81.8% (27/33)	91.5% (43/47)	50.0% (1/2)
AF Free @ >=12 months, off AADs	62.2% (28/45)	--	45.8% (11/24)	84.8% (39/46)	0% (0/3)
AF Free @ >=12 months	73.3% (33/45)	--	66.7% (16/24)	91.3% (42/46)	0% (0/3)

5. POST-APPROVAL STUDY

The current post-approval study proposes to assess the rate of freedom from AF (off AADs) at 3 years and the rate of device- and ablation procedure-related serious adverse events within 30 days.

Q5a. The sponsor proposes an effectiveness success criterion of 47.8% free of AF, off AADs at three years. Please comment of whether the proposed success criterion is clinically acceptable in that it represents a clinical benefit that compares favorably when compared against the risks of the device.

Q5b. The sponsor proposes a serious ablation procedure- and device-related adverse event rate of 17.5%. Please comment on using the serious ablation procedure- and device-related adverse event rate as the primary safety measure for the PAS, as opposed to the overall MAE rate that was used as the primary safety measure in the pivotal study. Please also comment on whether the proposed safety success criterion represents a level of risk that is clinically acceptable when compared against the benefits of the device.

Q5c. The sponsor proposes that individual investigators will determine whether safety events are related to the device or ablation procedure. Please comment on whether a Clinical Events Committee is necessary to adjudicate the ablation procedure- and device-relatedness of serious adverse events.

6. SAFETY AND EFFECTIVENESS

Q6. Based on the ABLATE study results and additional data provided, please discuss whether the overall picture provides a reasonable assurance of safety and effectiveness for the use of the AtriCure Synergy Ablation System for the proposed indication in the intended population. Please discuss all key factors that influence your assessment.